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(54) Title: A COMPOSITION COMPRISING AN ACTIVE AGENT DISSOLVED IN A GLASS-FORMING CARRIER AND A PROCESS FOR THE PREPARATION THEREOF

(57) Abstract

A biologically active composition comprising a solution of an active agent dissolved in a glass-forming carrier, which carrier comprises a glass-forming substance (A) containing a plasticizer (B), the amount of plasticizer preferably being selected so that the composition has a non-solid consistency. The composition can be prepared by dissolving the active agent in a melted mixture of the glass-forming substance and the plasticizer at a temperature below the decomposition temperature of said active agent. Use of the glass-forming carrier for dissolving a biologically active agent.

A COMPOSITION COMPRISING AN ACTIVE AGENT DISSOLVED IN A GLASS-FORMING CARRIER AND A PROCESS FOR THE PREPARATION THEREOF

Technical field

The present invention relates to the field of biologically active compositions and, in particular, to such a composition comprising a biologically active ingredient which, preferably, is a therapeutically active agent. However, other applications than within the medical field are also possible within the scope of the invention. More specifically the invention relates to a novel phase or formulation that is especially well adapted for formulating biologically active agents which are generally poorly water and fat soluble. Said novel formulation is potentially of great value because, by varying the composition thereof one can control the dissolution and/or release of the biologically active agent.

The invention also relates to said composition for use as a medicament as well as to a process for the preparation of said composition and to the use of a certain glass-forming carrier for a biologically active agent in a biologically active composition.

Background of the invention

In the development of novel medicines lately, great importance has been attached to creating as high uptake as possible of the active ingredient. Common to all medicines which are not administered by an injection is that they have to penetrate a biological membrane, e.g. the skin or the intestinal wall.

In the medical field the development of formulations for local or dermal applications has for many years primarily aimed at changing the properties of the skin so as to accomplish a more rapid penetration thereof. Research in the TDDS field, i.e. transdermal delivery systems, has

persion, the product manufactured being a solid powdery mass.

As prior art in connection with the invention reference can also be made to US-A-4,151,273 and US-A-4,938 964. US-A-4,151,273 discloses the use of a glassy matrix as a carrier for a drug but said carrier is more or less non-variably solid and used in a powdered product, e.g. a tablet, for oral administration. Moreover, it does not suggest the use of any plasticizer. US-A-4,938,964 discloses an adhesive carrier for ketoprofen, comprising a specific acrylic or methacrylic copolymer. Thus, also said carrier has a more or less fixed composition that does not enable any real compositional adjustments after the preparation thereof and is laminated on a solid film support. Furthermore, again, US-A-4,938,964 does not include any reference to a plasticizer.

Description of the invention

The present invention relates to a completely novel preparation or formulation for biologically active agents, and especially of the types referred to above, which may seem similar to the aforementioned solid dispersions, but which is of a completely different structure and thereby possessed of completely different properties as compared thereto. Although the ingredients used in the two cases are similar in their own right, the composition according to the present invention has been prepared in a completely different way to the previously known composition and, therefore, is of a completely novel structure and has different properties. More specifically, the composition according to the present invention is similar to a so called solid solution, i.e. the biologically active agent has been dissolved and not dispersed as in the prior art. By this novel measure it has been found possible to drastically increase or en-

Thus, it has now been found that a glass-forming carrier comprising a glass-forming substance and a plasticizer therefor can work excellently as a carrier for a biologically active agent in the formation of a biologically active composition showing outstanding characteristics.

More specifically the biologically active composition according to the present invention comprises a solution of a biologically active agent dissolved in a glass-forming carrier, which carrier comprises a glass-forming substance (A) containing a plasticizer (B).

That is, according to the invention it has been found that the new glass-forming carrier can dissolve a biologically active agent to a very great extent to the formation of a very versatile product provided specific considerations are made in connection with the glass-forming carrier and the preparation of the biologically active composition.

Thus, by means of the amount of plasticizer the consistency as well as activity characteristics of the composition can be controlled in a very simple way, contrary to the more or less fixed compositions in the prior art. According to a preferable embodiment of the invention this e.g. means that the composition comprises sufficient plasticizer to be non-solid at a temperature below the glass transition temperature (Tg) of the glass-forming substance alone.

Preferably the composition has a non-solid consistency at the intended use temperature of the composition and, optionally, at a temperature below 50°C, preferably below 40°C, more preferably within the range of -10°C to 50°C or -10°C to 40°C, and most preferably within the range of 0°C to 40°C.

The term non-solid should be interpreted in a broad sense and generally means liquid or jelly-like, where

a rigid or fixed composition dictated by the method of manufacturing the carrier matrix.

Although different processes for the preparation of compositions according to the invention will be more specifically described below, it can thus be emphasized at this stage that the invention is based on the idea of utilizing a combination of glass-forming substance and a plasticizer as a carrier for the biologically active ingredient. In this context the term glass is used in the meaning of an amorphous single phase mass consisting of one or more ingredients which are dissolved in each other.

At room temperature, such substances can be below their so called glass transition temperatures (Tg), but dissolving a biologically active agent in a pure glass-forming substance often requires the materials to be heated to such a high temperature that the active agent will start decomposing. Moreover, a glass is not stable, i.e. it will eventually crystallize. However, when adding the plasticizer to said substance, its Tg is reduced, providing a reduction in viscosity which enables the addition and dissolution of the active ingredient at a lower temperature, i.e. in practice at a temperature where decomposition does not take place. According to the invention it has furthermore been found that by means of the plasticizer the dissolution rate/release rate, and the consistency, of the composition can be varied or controlled.

At the temperature at which it is preferably used, a composition according to the invention is similar to a solid solution, which is generally defined as an amorphous solid phase mass of two or more components dissolved in each other but, as it is above its glass transition temperature, it differs therefrom by typically being a more or less viscous, often highly viscous, liquid,

some specific examples of interesting compounds are the antiviral compounds, especially guanoside compounds, such as acyclovir Vidarabin and Idoxuridin, and esters of antiviral substances, preferably fatty acid esters of antiviral guanoside derivatives; antimicrobial substances, such as e.g. erythromycin and metronidazol; antifungal compounds, e.g. griseofulvin and imidazoles; corticosteroids; vitamins; provitamins; hormones such as e.g. estradiol; antiinflammatory compounds, such as e.g. piroxicam, Indomethacin, clotrimazol or salicylic acid or derivatives thereof, e.g. acetylsalicylic acid and 4-5-aminosalicylic acid; flavonoids, such as e.g. Catechin, etc; anticancer agents, especially folic acid antagonists, e.g. metotrexate; and psychopharmaceutical drugs, e.g. Busulphan.

Generally these compounds have low water solubilities and in some instances, such as the guanoside compounds, can have polar properties in spite of said low water solubility. In this connection it should be noted that the term low water solubility, or similar, can not and need not be limited to specific figures, due to the nature of the invention. However, it can be added that such a compound as ketoprofen or similar may be excluded from the scope of protection according to one embodiment of the invention.

The glass-forming substance is generally selected from conventional substances having the ability to form a glass or, more specifically, a solid solution of the type defined above. Specific consideration should be given to the fact that melting temperature, glass transition temperature (Tg) and viscosity should suit the selected biologically active compound and the use envisaged for the composition after the addition of the plasticizer. In other words a number of glass-forming substances would work according to the invention provided that the Tg re-

should be usable also in connection with internal plasticizers chemically reacted with the glass-forming substance to plasticize the same.

As has been mentioned, in preferred embodiments, the inventive composition is a medical or pharmaceutical composition. In such a case the composition can of course contain additives of those types which are conventionally used in pharmaceutical compositions. Specifically, since the composition when used as a medicinal is primarily intended for administration via the skin, a skin penetration-enhancing substance can be included therein. The main purpose of using such a substance is to change the properties of the skin or to improve the contact with the skin. Examples of suitable substances of this kind are oleic acid, oleyl alcohol, monoolein and/or salicylic acid. Also mono, di or triglycerides can be added to products for oral use for the purpose of utilizing the fat-absorption mechanisms of the body itself to increase the uptake of drug from the intestines. Thus, the composition can be used also for other administration routes than by dermal administration, such as for oral, buccal, vaginal, rectal, intranasal or intravaginal administration, provided provisions can be taken to adapt the liquid or gel consistency to such administrations. Other additives may be introduced into the composition for the purpose of altering the pH, osmolarity and other general properties of the composition in contact with biological fluids or for dissolution purposes. Preservatives may also be added to the composition in order to increase microbiological stability.

The combination of glass-forming substance and the plasticizer therefor should be selected in line with the principles given above such that proper glass transition temperature, consistency, release profile, etc. are obtained. Typically this means that the percentage of

Of the additives referred to above, the inclusion of a skin penetration-enhancing substance is especially preferred. Again the nature and amount of such a substance is easily chosen by a person skilled in the art so as to obtain a maximum or optimum effect. Typically said substance or any other additive is utilized in the range of 0-10% by weight, based on the total weight of the glass-forming carrier.

An especially preferred use of the composition according to the invention is, as was mentioned above, as a pharmaceutical composition. In this case the biologically active agent is of course a therapeutic or prophylactic compound of any kind. The other ingredients of the composition are selected in accordance with the general principles for pharmaceutical compositions. However, the composition is of course utilizable in all applications where it is desired to solubilize agents, especially such agents which are poorly water or fat soluble per se.

In an especially preferred embodiment the inventive composition comprises a medicament for administration to the skin, or for dermal administration. In such a case a person skilled in the art will formulate the composition such that its viscosity will be proper for administration in that way and so that the release of the active compound will have the desired profile. By varying the composition in this way one can, thus, easily and effectively control the release both as regards the time profile and the amount profile, to achieve a controlled or sustained release, which of course also applies to other administrations than dermal administration.

According to another embodiment of the invention the composition claimed is adapted for an oral or buccal administration thereof. The composition is then preferably prepared in such a way that the viscosity of the preparation allows for a filling in hard or soft gelatine cap-

(C) or any other additive can be dissolved in the single phase mass.

In a preferred embodiment, the glass-forming substance is heated to a temperature above its melting point and the plasticizer is added to the melted mass, or the glass-forming substance is heated together with the plasticizer to form an amorphous single phase mass in the melted state. Typically, the temperature to which the mixture of the glass-forming substance with the plasticizer, prior to dissolution, is heated, is too high to enable the direct addition of the biologically active agent without causing it to decompose. Preferably, therefore, the melted mass is firstly cooled to a temperature at which the active agent can still be added and dissolved. The presence of the plasticizer reduces the viscosity and thereby a rapid dissolution of the active agent can be obtained at a lower temperature than if a pure glass-forming substance were utilized.

The resulting solution, which includes the biologically active agent dissolved in the amorphous mass, is then preferably cooled down to the desired storage or use temperature. Said storage or use temperature is, as was mentioned above, still above, and preferably substantially above, the glass transition temperature of the composition, as the risk of causing crystallization, thus, is thereby avoided or essentially eliminated. Compositions prepared by the inventive process, therefore, possess a high stability.

As should be clear from the description above one of the advantages of the invention is that it does not involve the use of water and/or any volatile organic solvent in the manufacturing process. Consequently the composition claimed is substantially free of water and/or volatile organic solvent.

eral instructions in this respect are not easily given. Typically, however, the initial melting operation is performed at a temperature in the range of 90-170°C, preferably 105-160°C, and the molten carrier is then cooled down to a temperature in the range of 60-120°C, preferably 80-110°C, before the biologically active agent is dissolved therein.

Finally, still another aspect of the invention is the use of the glass-forming carrier as defined above for dissolving a biologically active agent in the formation of a biologically active composition.

Preferable embodiments of said use are similar to the preferable embodiments described above in connection with the composition or process and need not be repeated once more.

EXAMPLES

The invention will now be exemplified further by means of the following non-limiting working examples, wherein the commercial preparation referred to was Zovirax cream (a cream containing 5% of acyclovir).

EXAMPLE 1

4g of citric acid and 4 g of glycerol were heated to 160°C and admixed to a homogenous mass. Said mixture was allowed to cool down to 80°C. In the meantime 0.5g of acyclovir was stirred into glycerol heated to 80°C to form a suspension of acyclovir in glycerol. Said suspension was in turn stirred into the first melt of citric acid and glycerol, the temperature still being 80°C. The stirring operation was continued until the suspension became clear, whereupon the solution obtained was cooled down to room temperature. Thus, firstly this experiment shows that it is possible to dissolve 5% by weight of acyclovir into a viscous liquid solid" solution in accordance with the invention.

4g of citric acid was mixed at 80°C with 4g of propylene glycol. In the meantime 0.5g of acyclovir was admixed with 1.5g of propylene glycol at the same temperature. The two products were then mixed with each other, the temperature still being maintained at 80°C.

20g of white petrolatum was heated to 60°C, whereupon the solution of acyclovir in citric acid and propylene glycol was added to the petrolatum. The internal phase, comprising the solution of acyclovir in citric acid and propylene glycol, was homogenized to a proper drop size and the temperature of the resulting formulation was reduced down to 25°C with continued stirring.

EXAMPLE 5

5,9 g of citric acid and 3,7 g of propylene glycol were heated to 110°C and admixed to a homogeneous mass. When said mixture was clear, 0,2 g of oleoyl alcohol and Brij 98 were added and when a clear solution was obtained said solution was cooled to 100°C.

0,12 g of griseofulvin was then added and after a clear solution had been obtained this was cooled to room temperature to provide a viscous liquid solution containing 1,2% of griseofulvin.

EXAMPLE 6

Acyclovir	0,75 g
Citric acid	4,0 g
Polyethylene glycol	5,5 g

The preparation is made in accordance with Example 2 and after cooling to room temperature the viscous product is filled onto hard gelatine capsules.

EXAMPLE 7

Metronidazol	1 g
Citric acid	8 g
Polyethylene glycol	2 g

CLAIMS

1. A biologically active composition comprising a solution of a biologically active agent dissolved in a glass-forming carrier, wherein the glass-forming carrier comprises a glass-forming substance (A) containing a plasticizer (B).

2. A composition as claimed in claim 1, comprising sufficient plasticizer (B) to be non-solid, preferably liquid or jelly-like, at a temperature below the glass transition temperature (Tg) of the glass-forming substance (A) alone.

3. A composition as claimed in claim 2, having a non-solid consistency, preferably liquid or jelly-like, at the intended use temperature of the composition and, optionally, at a temperature below 50°C, preferably below 40°C, more preferably within the range of -10°C to 40°C and most preferably within the range of 0°C to 40°C.

4. A composition as claimed in any one of the preceding claims, wherein the glass transition temperature (Tg) of the carrier allows for a dissolution of said biologically active agent at a temperature where significant decomposition of said agent is avoided.

5. A composition as claimed in any one of the preceding claims, wherein the glass transition temperature (Tg) of the solution allows for the manufacture of a stable solution without any significant decomposition of the biologically active agent and allows for a stable solution at use and/or storage.

6. A composition as claimed in any one of the preceding claims, wherein significant thermally induced decomposition of the biologically active agent is avoided in a temperature range extending up to a temperature

17. A composition as claimed in any one of the preceding claims, wherein the glass-forming substance is selected from mono and oligosaccharides, and polymers and polyalkylene glycols, which preferably have a Tg above 0°C.

18. A composition as claimed in any one of claims 1 - 16, wherein the glass-forming substance comprises citric acid.

19. A composition as claimed in any one of the preceding claims, wherein the plasticizer (B) is selected from alcohols, carbonates, low molecular weight polymers and organic acids.

20. A composition as claimed in claim 19, wherein said plasticizer is selected from glycerol, propylene glycol, dipropylene glycol, propylene carbonate and lactic acid.

21. A composition as claimed in any one of the preceding claims, which further contains a skin penetration-enhancing substance (C).

22. A composition as claimed in claim 21, wherein said skin penetration-enhancing substance (C) is selected from oleic acid, oleyl alcohol, monoolein and salicylic acid.

23. A composition as claimed in any one of the preceding claims, which further contains a mono, di, or triglyceride acting as a fat-absorption enhancing substance to increase the uptake of the biologically active agent from the intestines.

24. A composition as claimed in any one of the preceding claims, wherein the amount of glass-forming substance (A) is in the range of 10-90, preferably 20-80, and more preferably 30-70, percent by weight and the amount of plasticizer (B) is in the range of 90-10, pref-

forming carrier and dissolving the biologically active agent in the molten carrier at a sufficiently low temperature to prevent significant decomposition of said active agent.

33. A process as claimed in claim 32, wherein the molten carrier is cooled to below the decomposition temperature of the active agent before said active agent is dissolved therein.

34. A process as claimed in claim 32 or 33, wherein the biologically active composition is as claimed in any one of claims 2-31.

35. A process as claimed in any one of claims 32-34, wherein the molten carrier is an amorphous single phase mass.

36. A process as claimed in claim 35, wherein a mixture of the glass-forming substance (A) and the plasticizer (B) is melted to form the amorphous mass.

37. A process as claimed in any one of claims 32-36, wherein the biologically active agent is dissolved in the molten carrier by adding the same in powdered form directly to said molten carrier.

38. A process as claimed in any one of claims 35-36, wherein the biologically active agent is dissolved in the amorphous mass by firstly dissolving or suspending the same in a part of the plasticizer (B) and then adding the solution or suspension obtained thereby to said amorphous mass.

39. A process as claimed in any of claims 32-38, wherein the initial melting operation is performed at a temperature in the range of 90-170°C, preferably 105-160°C, and the molten carrier is then cooled down to a temperature in the range of 60-120°C, preferably 80-110°C, before dissolving the biologically active agent therein.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/00806

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/06, A61K 9/00, A61K 47/12
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, BIOSIS, MEDLINE, WPI, WPIL, CLAIMS, INSPEC, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4151273 A (SIDNEY RIEGELMAN ET AL), 24 April 1979 (24.04.79), column 1, line 65 - line 68; column 2, line 25 - line 52	1-45
X	US 4938964 A (YASUYUKI SAKAI ET AL), 3 July 1990 (03.07.90), column 5, line 58 - column 7, line 58, claims	1-45
A	WO 9311749 A1 (WARNER-LAMBERT COMPANY), 24 June 1993 (24.06.93), claims	1-45

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

Information on patent family members

05/09/96

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4151273	24/04/79	NONE	
US-A- 4938964	03/07/90	EP-A- 0319988	14/06/89
		JP-A- 1250317	05/10/89
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